

REMARKS

Claims 1, 2, 4-15, 20-24, 26 and 27 are pending and rejected.

New claims 28-31 and find support throughout the application as originally, especially in Table 1 (pages 83-84), which lists numerous compounds that inhibit EIF2C1 expression “by at least 60% [80%]”.

Upon entry of this amendment, claims 1, 2, 4-15, 20-24, 26-31 will be pending.

No new matter has been added.

Rejections under 35 U.S.C. § 112

Claim 20 was again rejected and claims 21-24, 26 and 27 were newly rejected under 35 U.S.C. § 112, first paragraph, because allegedly “the specification while being enabling for antisense-mediated inhibition of EIF2C1 expression *in vitro*, does not reasonably provide enablement for *in vivo* antisense-mediated modulation of endogenous RNA-mediated interference pathway.” (Office Action, page 2). The Office alleges that the use of antisense compounds *in vivo* is unpredictable and is not enabled by the present application. Applicants respectfully disagree and assert that the claimed invention is enabled.

The present application teaches the skilled artisan how to make and use the claimed invention. The crux of the rejection set forth by the Office appears to be that the present application, and also the prior art, allegedly does not support a correlation of *in vitro* results with *in vivo* results, especially when there are no working examples in the present application to support *in vivo* claims. In support of its allegation that the field of antisense is unpredictable, the Office cited Crooke *et al* (Crooke *et al.*, (1998) *Handbook of experimental pharmacology*, vol. 31: Ch. 1 Antisense Research and Application, pp. 1-50, hereinafter the “Crooke reference”) and Gewirtz *et al*. (Gewirtz *et al.*, (1996) *PNAS*, 93:3161-3163, hereinafter, the “Gewirtz reference”). Neither the Crooke reference nor the Gewirtz reference, however, supports the Office’s position.

Applicants respectfully assert that the Office has mischaracterized the Crooke and Gewirtz references. The Office directed Applicants to a passage in the Crooke reference that states, “extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate ... one cannot predict *in vivo*

pharmacokinetics of the compounds based on *in vitro* studies." (Crooke, p. 3). According to the Office, "the reasoning in this passage, it follows that any oligo which is taken up by a cell *in vitro*, even if it proceeds to inhibit a target, that no meaningful prediction can be made was to whether the oligo will ever be taken by cells *in vivo*." (Office Action, page 4). This is not an accurate characterization of the cited passage. The passage discusses how the pharmacokinetic properties of a compound *in vitro* correlates to pharmacokinetic properties *in vivo*. The passage does not discuss whether or not compounds will be taken up by cells *in vivo*. Pharmacokinetics is the study of what the body does to a compound, which includes, among other activities, uptake, metabolism, function, and other properties of a compound *in vivo*. Although, the pharmacokinetics of a compound *may* be different *in vitro* and *in vivo*, the Crooke reference does *not* teach that the compounds will *not* be taken up *in vivo* or that the compounds will *not* work *in vivo*. However, even a suggestion that one cannot be 100% certain when extrapolating *in vitro* data to *in vivo* results is irrelevant to the issue of *in vivo* enablement. An ability to make an absolutely certain prediction is not required for patentability. Enablement does not require 100% predictability, a reasonable amount is adequate and it is the state of the art is at the time of filing that is important, not just what one or two references discuss. *See Cross v. Iizuka*, 753 F.2d 1040, 1050, 224, USPQ 739, 747 (Fed. Cir. 1985)

With respect to the Gewirtz reference, the Office cites the statement by the author "while the application of GS2888 to cell culture experiments has been clearly demonstrated, its utility for therapeutic applications *remains to be determined*." Preliminarily, Applicants point out that GS2888 is an entirely different chemical entity than the presently claimed compounds of the claimed invention. GS2888 is not a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding EIF2C1 nor is it an antisense oligonucleotide. Instead, GS2888 is a transfection reagent. Whether or not GS2888 will work in therapeutic applications is irrelevant to the patentability of the present claims. Notwithstanding the foregoing, the cited passage does not teach that the tested agent will not work *in vivo*; rather, the passage makes clear that as of the publication date of the Gewirtz reference, the authors saw a need for further studies to determine whether or not GS2888 will work *in vivo*. The use of GS2888 in

therapeutic applications has no bearing on the correlation of inhibition results *in vitro* to *in vivo* for nucleobase-based compounds.

The M.P.E.P. discusses the issue of correlation of *in vitro* and *in vivo* data and makes clear that it is the **overall the state of the art** that is important for determining the unpredictability of a field, not one or two references. The M.P.E.P. states:

In this regard, the issue of 'correlation' is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, *the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition.* In *re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications)...*A rigorous or an invariable exact correlation is not required* as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224, USPQ 739, 747 (Fed. Cir. 1985).

(M.P.E.P. 2164.02, emphasis added). It appears that the Office is under the impression that an "exact correlation" is required, while the M.P.E.P. clearly states that it is not.

Moreover, the Office has failed to take into account numerous references which more accurately describe the status of the field of antisense technology at or prior to the filing date of the present application (November 8, 2001). Indeed, the state of the prior art as a whole does not support the Office's position. A recent survey of the relevant scientific literature demonstrates that there is a correlation between *in vitro* results and *in vivo* data in the field of the present invention and that *in vivo* use is not unpredictable. This survey demonstrates numerous examples of correlation between *in vitro* experiments and *in vivo* experiments. For example, in Smith *et al.* (*Clinical Cancer Research*, 7:400-406, February 2001), data is discussed demonstrating inhibition of bcl-2 expression *in vitro* and *in vivo*. In Dwyer *et al.* (*Clinical Cancer Research*, 5: 3977-3982, December 1999), the administration of an antisense compound inhibited the expression of *c-raf-1* mRNA *in vitro* and *in vivo*. Based on these results the authors performed a clinical trial in human patients where expression of *c-raf-1* was inhibited. In Miyake *et al.*, (*Clinical Cancer Research*, 6:1655-1663, May 2000) the authors provide data that demonstrate the

inhibition of TRPM-2 both *in vitro* and *in vivo*. In Wang *et al.*, (*Clinical Cancer Research*, 7:3613-3624, November 2001) the authors discussed *in vitro* inhibition of *mdm-2* expression followed by data demonstrating *in vivo* inhibition of *mdm-2* expression. In Berg *et al.*, (*The Journal of Pharmacology and Experimental Therapeutics*, 298:477-484, 2001) the authors demonstrate *in vitro* and *in vivo* inhibition of thymidylate synthase expression. Tortora *et al.* (*Clinical Cancer Research*, 7:2537-2544, August 2001) discusses results where antisense oligonucleotide against protein kinase alpha type I (PKAI) inhibit expression *in vitro* and show antitumor activity *in vivo*. In Tortora the authors combine PKAI antisense compounds with bcl-2 antisense compounds and demonstrate *in vitro* inhibition. Significantly, Tortora also demonstrates anti-tumor activity *in vivo* characterized by reduced tumor volume and increased survival, which was assumed to be due to the inhibition of PKAI and bcl-2. *Id.* In Olson *et al.* (*Clinical Cancer Research*, 7:3598-3605, November 2001), inhibition of human angiogenin expression is described *in vitro* and *in vivo*. Applicants attach hereto copies of the above-identified references along with other references that demonstrate a correlation between *in vitro* and *in vivo* data. These articles and others available in the art demonstrate that a person of ordinary skill in the art would accept that *in vitro* inhibition of a specific gene's expression *does* correlate with *in vivo* inhibition.

Thus, when taken as a whole, including the references cited by the Office, the state of the art at the time of the application's filing, does *not* support the Office's allegation that the field of antisense is unpredictable and that there is no correlation between *in vitro* and *in vivo* results.

In addition, Applicants respectfully remind the Office that the absence of working examples "should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement," and "the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970))." (M.P.E.P § 2164.02) Applicants further point out that a determination whether *in vivo* data is sufficient for a drug approval by the Food and Drug Administration is not the same as a determination whether a correlation exists between *in vitro* and *in vivo* data for patentability purposes. ((See, M.P.E.P. 2164.05,

“considerations made by the FDA for approving clinical trials are *different* from those made by the PTO in determining whether a claim is enabled.”) (citations omitted, emphasis added)).

It appears that the Office is under the impression that the references cited in the Office Action do not focus on *in vivo* results because, “there simply is not much to say on the subject, because there is so little to discuss.” (Office Action, page 6). However, the decision of the authors of the references not to comment on the subject is not evidence that the claimed invention is not enabled. The absence of a positive result is not evidence of a negative result. The Office has provided no reason or evidence to doubt the objective truth of Applicants’ assertion that the invention is enabled. That the references cited by the Office are silent with respect to a particular issue simply is not the evidence that the law requires the Office to proffer.

Therefore, the overall state of the art in the field of antisense does not teach that antisense technology *in vivo* is unpredictable. One of ordinary skill in the art would not agree with the Office’s unsupported assertion that *in vitro* data does *not* correlate with *in vivo* data. Indeed, the Office has not provided any concrete evidence that the claimed invention is not enabled. Thus, the specification enables the pending claims of the present application.

Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1, 2, and 4-15 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Koesters *et al.*, (*Genomics*, 61:210-218, hereinafter the “Koesters reference”) in view of Taylor *et al.* (*Drug Discovery Today*, 4:562-567, hereinafter the “Taylor reference”), Baracchini *et al.* (U.S. Patent No. 5,801,154, hereinafter the “154 patent”), and Milner *et al.*, (*Nature Biotechnology*, 15:537-540). Applicants respectfully disagree because the Office has failed to establish a *prima facie* case of obviousness. In addition, the Examiner has failed to provide any motivation to modify the cited references so as to render the present claims obvious.

To support a conclusion that a claimed combination is directed to obvious subject matter, either the references must expressly or implicitly suggest the claimed combination or the Examiner must present a convincing line of reasoning as to why the skilled artisan would have found the claimed invention obvious in light of the teachings of the references. Further, the Examiner is prohibited from basing an obviousness rejection on hindsight reconstruction by including knowledge "gleaned only from applicants disclosure . . ." *In re McLaughlin*, 170 USPQ 209, 212 (CCPA 1971).

As is clear from MPEP §2143, in order to provide a *prima facie* case of obviousness, the Examiner must first establish motivation to combine or modify the references.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP §2143. The Examiner cannot rely upon a reasonable expectation of success alone to establish motivation. Such reliance is improper.

The Federal Circuit has recently affirmed the requirement for motivation to combine references, stating that:

virtually all [inventions] are combinations of old elements. Therefore, an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed [**10] elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention

...

To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and *with no knowledge of the claimed invention*, would select the elements from the cited prior art references for combination in the manner claimed . . .

To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Yamanouchi Pharm. Co. v. Danbury Pharm, Inc., 231 F.3d 1339 (Fed. Cir. 2000); 56 U.S.P.Q.2D 1641, 1645, citing *In re Rouffet*, 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457-8 (Fed. Cir. 1998) (emphasis added).

It appears that the Examiner has done what Yamanouchi reaffirms should not be done—used Applicants' specification as a blueprint.

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been led to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from appellants' disclosure, see for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references."

... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would impel one skilled in the art to do what the patent applicant has done. (citations omitted; emphasis added)

Significantly, the Office Action identifies no "motivating force" that would "impel" persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention.

Cited References

The Koesters reference discusses EIF2C1 but fails to teach or even suggest a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding EIF2C1 (SEQ ID NO:3), wherein the compound specifically hybridizes with the nucleic acid molecule encoding EIF2C1 and inhibits the expression of EIF2C1. Furthermore, the Koesters reference fails to teach or even suggest the elements of the claims dependent on claim 1. For example, Koesters fails to teach embodiments of claim 1 wherein the compounds are antisense oligonucleotides, wherein the compounds comprise at least one modified internucleoside linkage, at least one modified sugar moiety, at least one modified nucleobase, and/or the antisense oligonucleotide is a chimeric oligonucleotide. The Koesters reference also fails to teach compounds 8 to 50 nucleobases in length which specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding EIF2C1. The Koesters reference also fails to teach a composition comprising the compound of claim 1 and pharmaceutically acceptable carrier or a method of inhibiting the expression of EIF2C1 in cells or tissues comprising contacting the cells or tissues with the compound of claim 1 so that the expression of EIF2C1 is inhibited. Koesters further fails to teach the subject matter of new claims 28 and 29, *i.e.*, embodiments wherein the modulation of EIF2C1 expression is at least 60% or 80%.

The Taylor reference fails to compensate for the deficiencies of the Koesters reference. Taylor discusses antisense oligonucleotides and a systematic high-throughput approach to target validation and gene function determination but fails to teach or even suggest a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding EIF2C1 (SEQ ID NO:3), wherein the compound specifically hybridizes with the nucleic acid molecule encoding EIF2C1 and inhibits the expression of EIF2C1. Indeed, Taylor fails to even discuss the EIF2C1 gene, much less compounds that target and inhibit EIF2C1 expression. Furthermore, Taylor fails to teach or suggest the elements of the claims dependent on claim 1, as discussed above.

The '154 patent discusses antisense oligonucleotide modulation of multidrug resistance-associated protein but fails to compensate for the deficiencies of the Koesters reference and the Taylor reference. The multidrug resistance-associated protein is not

equivalent or even related to EIF2C1. The '154 patent fails to teach or even suggest a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding EIF2C1 (SEQ ID NO:3), wherein the compound specifically hybridizes with the nucleic acid molecule encoding EIF2C1 and inhibits the expression of EIF2C1. The '154 patent fails to even discuss the EIF2C1 gene, much less compounds that target and inhibit EIF2C1 expression. Furthermore, the '154 patent fails to teach or suggest the elements of the claims dependent on claim 1, as discussed above.

The Milner reference discusses the selection of effective antisense reagents on combinatorial oligonucleotide arrays but fails to compensate for the deficiencies of the Koesters reference, the Taylor reference and the '154 patent. The Milner reference fails to teach a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding EIF2C1 (SEQ ID NO:3), wherein the compound specifically hybridizes with the nucleic acid molecule encoding EIF2C1 and inhibits the expression of EIF2C1. Indeed, Milner fails to even discuss the EIF2C1 gene, much less compounds that target and inhibit EIF2C1 expression. Furthermore, Milner fails to teach or suggest the elements of the claims dependent on claim 1, as discussed above.

The Office has failed to provide motivation to combine the cited references

None of the references cited in the Office Action suggest using compounds 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding EIF2C1 (SEQ ID NO:3), wherein the compound specifically hybridizes with the nucleic acid molecule encoding EIF2C1 and inhibits the expression of EIF2C1. None of the references cited by the Office suggest modifying any reference or any composition as to yield the claimed invention. Additionally, none of the references cited by the Office suggest making and/or using such a compound that specifically hybridizes with a nucleic acid molecule encoding EIF2C1 comprising at least one modified internucleoside linkage, an antisense oligonucleotide, a modified internucleoside linkage that is a phosphorothioate linkage, at least one modified sugar moiety, a 2'-O-methoxyethyl sugar moiety, at least one modified nucleobase, 5-methylcytosine, or a chimeric oligonucleotide and that inhibits the expression of EIF2C1. Of the four references cited by the Office, only one even identifies the EIF2C1 gene.

There is no motivation within the references, nor has one been identified by the Office, to combine the references in the manner suggested in the Office Action in such a way as to yield the claimed invention. The references do not refer to one another either explicitly or implicitly. It appears that the only motivation that the Office is using to combine the references is the use of the Applicants' specification and hindsight reconstruction, which is strictly forbidden. Accordingly, the combination of references is improper for its use of hindsight reconstruction based upon Applicants' disclosure.

“Obvious to Try” Is Not a Substitute for Motivation to Combine

The Office Action makes a general statement that it would be obvious to combine teachings of a single reference with a limited discussion of EIF2C1 with references that discuss various antisense issues. Such a generalized motivation *is not* a “motivating force” that would “impel” persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention. Such a statement, at most, raises an inappropriate “obvious to try” standard. Indeed, the court made it clear that it is improper to reject claims as “obvious to try” where the motivation to combine references arises merely because the subject matter of the claimed invention is a promising field for experimentation, although the prior art provides only general guidance as to particular form of the claimed invention or how to achieve it. *In re O’Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Without more specific suggestions in the prior art, there is insufficient motivation to combine the cited references. Furthermore, “focusing on the obviousness of substitutions and differences, instead of the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness.” *Gillette Co. v. S.C. Johnson & Son*, 16 U.S.P.Q.2d 1923, 1927 (Fed. Cir. 1990). If the Examiner’s reasoning was used to its logical conclusion, then no antisense molecules would ever be non-obvious if a particular target were known. Thus, only newly identified genes could ever provide non-obvious antisense molecules. The law does not support the Examiner’s reasoning.

When assessing whether or not a combination of references would have produced a claimed invention, one must consider the teaching of each reference as a whole without undue emphasis on those features that would support a finding of

obviousness. *In re Wesslau*, 147 U.S.P.Q. 391 (C.C.P.A. 1965) (it is impermissible to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what the references fairly suggest to one of ordinary skill in the art). Consideration of the cited references as a whole for what they each fairly suggest, demonstrates that a person of ordinary skill seeking to combine them would *not* have produced any claimed invention. In this respect, the Office Action has apparently picked one particular element from the Koesters reference, one particular element from the Milner reference, one particular element from the '154 patent, and one particular element from the Taylor reference. One skilled in the art, however, would *not* be motivated to pick and choose only those specific elements referred to in the Office Action from the many elements recited in the cited references and combine the selected elements in the specific manner indicated in the Office Action, without regard to the many other elements present in the references. Indeed, it appears that the only guide to picking and choosing particular elements from the cited art of records appears to have been the present application. Thus, the combination of references is improper for, at the very least, failure to provide motivation to combine references and for its use of hindsight reconstruction based upon Applicant's disclosure.

Thus, in view of the foregoing, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness. In particular, the Office has failed to provide any motivation that would *impel* one skilled in the art to modify the cited references so as to produce Applicant's claimed inventions. Indeed, the Office has failed to provide the requisite motivation to modify the cited references so as to arrive at the claimed invention.

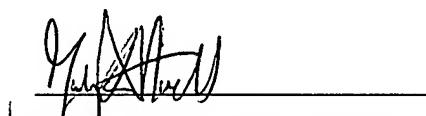
Accordingly, Applicants respectfully request the rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Conclusion

Applicants believe the pending claims are in condition for allowance. An early Notice of Allowance is therefore earnestly solicited. Applicants invite the Examiner to contact the undersigned at (215) 665-6904 to clarify any unresolved issues raised by this response.

Respectfully submitted,

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Attachments: Smith *et al.* (*Clinical Cancer Research*, 7:400-406, February 2001)
Dwyer *et al.* (*Clinical Cancer Research*, 5: 3977-3982, December 1999)
Miyake *et al.*, (*Clinical Cancer Research*, 6:1655-1663, May 2000)
Wang *et al.*, (*Clinical Cancer Research*, 7:3613-3624, November 2001)
Berg *et al.*, (*The Journal of Pharmacology and Experimental Therapeutics*, 298:477-484, 2001)
Tortora *et al.* (*Clinical Cancer Research*, 7:2537-2544, August 2001)
Olson *et al.* (*Clinical Cancer Research*, 7:3598-3605, November 2001)